Comparative Effectiveness of 12 Treatment Strategies for Preventing Contrast-Induced Acute Kidney Injury: A Systematic Review and Bayesian Network Meta-analysis

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Abstract

Background: To simultaneously evaluate the relative efficacy of multiple pharmacological strategies for preventing contrast-induced acute kidney injury (CI-AKI).

Study Design: Systematic review containing a Bayesian network meta-analysis of randomized controlled trials (RCTs)

Setting & Population: Participants undergoing diagnostic and/or interventional procedures with contrast media.

Selection Criteria for Studies: RCTs comparing the active drug treatments with each other or with hydration alone.

Intervention: Any of the following drugs in combination with hydration: N-acetylcysteine (NAC), theophylline (aminophylline), fenoldopam, iloprost, alprostadil, prostaglandin E1, statins, statins plus NAC, bicarbonate sodium, bicarbonate sodium plus NAC, ascorbic acid (vitamin C), tocopherol (vitamin E), alpha lipoic acid, atrial natriuretic peptide, B-type natriuretic peptide, and carperitide.

Outcomes: The occurrence of CI-AKI

Results: The trial network included 150 trials with 31,631 participants and 4,182 CI-AKI events assessing 12 different interventions. Compared with hydration, the odds ratios (ORs) for CI-AKI were 0.31 (95% credible interval 0.14 to 0.60) for high-dose statin plus NAC, 0.37 (0.19 to 0.64) for high-dose statins alone, 0.37 (0.17 to 0.72) for prostaglandins, 0.48 (0.26 to 0.82) for theophylline, 0.62 (0.40 to 0.88) for bicarbonate sodium plus NAC, 0.67 (0.54 to 0.81) for NAC alone, 0.64 (0.41 to 0.95)
for vitamins and its analogues, 0.70 (0.29 to 1.37) for natriuretic peptides, 0.69 (0.31 to 1.37) for fenoldopam, 0.78 (0.59 to 1.01) for bicarbonate sodium, and 0.98 (0.41 to 2.07) for low dose statin. High-dose statin plus NAC or high-dose statin alone were likely to be ranked the best or the second best for preventing CI-AKI. The overall results were not materially changed in meta-regressions, subgroup and sensitivity analyses.

**Limitations:** Patient-level data was unavailable. Unable to include some treatment agents, low event rates, and imbalanced distribution of participants among treatment strategies.

**Conclusions:** High-dose statins plus hydration with or without NAC might be the preferred treatment strategy to prevent CI-AKI in patients undergoing diagnostic and/or interventional procedures requiring contrast media.

**Index Words:** contrast-induced acute kidney injury (CI-AKI), contrast media, kidney disease, acute kidney failure, statins, hydroxymethylglutaryl-CoA reductase inhibitor, atorvastatin, rosvastatin, simvastatin, serum creatinine, cardiovascular events, systematic review.
Introduction

With the steady increase in the rates of diagnostic and/or interventional procedures with contrast media (CM), contrast-induced acute kidney injury (CI-AKI) has become the third most common cause of AKI in hospitalized patients.\textsuperscript{1} CI-AKI leads to prolonged hospitalization, increased costs, and increased morbidity and mortality.\textsuperscript{2}

Factors associated with the risk of CI-AKI include pre-existing renal functional impairment, diabetes, hypertension, chronic heart failure, advanced age, volume depletion, haemodynamic instability, use of concurrent nephrotoxic medications, and large volume or high osmolality of CM.\textsuperscript{3,4}

Minimization of the CM dose and the use of iso-osmolar or low-osmolar CM are recommended as non-pharmacological precautions, and numerous pharmacological strategies for preventing CI-AKI have been evaluated. In 2008, a comprehensive meta-analysis of randomized controlled trials (RCTs) concluded that N\textsubscript{acetylcysteine} (NAC) in combination with hydration was more effective than hydration alone.\textsuperscript{5}

However, due to the lack of head-to-head comparisons between treatment agents, traditional pairwise meta-analyses could not be used to simultaneously synthesize all evidence and generate clear hierarchies for the efficacy of different treatments.\textsuperscript{5-8}

Therefore, the choice of the best treatment in practice is generally based on subjective judgement, and objective information regarding the relative efficacy of different interventions would help the development of clinical practice guidelines for preventing CI-AKI.

Bayesian network meta-analysis, also known as mixed treatment comparison,
enables indirect comparison using a common comparator, and combines direct and indirect comparisons to synchronously assess multiple treatments. \(^9\)–\(^{11}\) The usefulness of this method has been demonstrated in many studies on various medical conditions and interventions. \(^{12}\)–\(^{14}\) This systematic review and network meta-analysis therefore aims to compare the relative efficacy of different pharmacological interventions for preventing CI-AKI by means of network meta-analysis within a Bayesian framework.

**Methods**

**Data Sources and Searches**

This systematic review was performed according to a pre-specified protocol (Item S1) and the reporting was in line with PRISMA guidelines. \(^{15}\) We searched MEDLINE via Ovid (from 1946 to May 2016), Embase (from 1966 to May 2016), and the Cochrane Library database (Cochrane Central Register of Controlled Trials; before May 2016) for RCTs of CI-AKI prevention, without any language restrictions (see Item S1 for full search terms). The ClinicalTrials.gov website was also searched for RCTs that were registered as completed but not yet published.

**Study Selection**

We included RCTs that evaluated any of the following drugs in combination with hydration: NAC, theophylline (aminophylline), fenoldopam, iloprost, alprostadil, prostaglandin E1, statins, statins plus NAC, bicarbonate sodium, bicarbonate sodium plus NAC, ascorbic acid (vitamin C), vitamin E or its analogues (tocopherol), alpha
lipoic acid, atrial natriuretic peptide, B-type natriuretic peptide, and carperitide. RCTs comparing the above active drug treatments with each other or with hydration were eligible. We excluded studies that contained only one or none of the above treatments. Eligible participants were those who underwent diagnostic and/or interventional procedures with CM, such as diagnostic coronary or peripheral arterial angiography or percutaneous intervention, ventriculography, enhanced CT, intravenous pyelography, and other relevant procedures.

The treatment groups were classified into 12 categories according to the drug species and/or dose: 1. atrial natriuretic peptide, B-type natriuretic peptide and carperitide were classified into natriuretic peptide; 2. ascorbic acid (vitamin C, tocopherol and alpha-lipoic acid were classified into vitamins and its analogues; 3. simvastatin 40-80 mg, rosuvastatin 20-40 mg and atorvastatin 40-80 mg were known as high-dose statin; 4. low-dose statin included simvastatin 10-20 mg, rosuvastatin 10 mg and atorvastatin 10-20 mg; 5. iloprost, alprostadil, misoprostol and prostaglandin E1 were categorized into prostaglandin. The other seven treatments included: 6. theophylline (aminophylline); 7. NAC; 8. fenoldopam; 9. bicarbonate sodium; 10. bicarbonate sodium plus NAC; 11. high-dose statin plus NAC; 12. hydration

Data Extraction and Quality Assessment

Study selection, data extraction, and quality assessment were performed independently by two investigators (XL.S and XF.X) according to the pre-specified study protocol (Item S1). The two investigators screened the titles and abstracts of the records identified by the search strategies for eligibility. Disagreements were resolved...
by discussion with a third reviewer (LJ.L). Data on pre-specified variables from the
included studies were extracted into a computerized spreadsheet.

The outcome used was the development of CI-AKI, defined as an absolute increase in
the baseline serum creatinine level of greater than 44.2 μmol/L (0.5 mg/dL) or a
relative increase of greater than 25%, typically within 48-72 h after contrast
injection.\textsuperscript{16,17} If data was not available for the first 48-72 h after the treatment, we
used data obtained within the first 5 days of treatment (the data point closest to 48-72
h was given preference).\textsuperscript{18} If different measurement index (eg. eGFR, Ccr) or standard
was applied, we extracted data according to one defined by authors of the included
studies.

We assessed sources of bias using the Cochrane Collaboration risk-of-bias tool,\textsuperscript{19}
including an assessment of financial conflicts of interest.\textsuperscript{20} We developed operational
definitions for high, low, and unclear risk of bias for each of the eight validity
domains (Item S2).

**Data Synthesis and Analysis**

We used odds ratio (OR) and its 95% credible intervals (CrIs) to measure the
relative effect of different treatments on CI-AKI outcome. Before conducting network
meta-analysis, we conducted conventional pairwise meta-analyses for treatments that
were directly compared in RCTs. We used fully Bayesian method (FB), assuming a
binomial likelihood on the log-odds scale, in pairwise meta-analyses through
WinBUGS 1.4.3.\textsuperscript{21,22} To investigate heterogeneity in conventional pairwise meta-
analysis, we used STATA 12.0 to conduct meta-regression of direct comparisons
based on empirical Bayes method, and estimated $I^2$, $\tau^2$ and $Q$ value.

Network meta-analysis was conducted by using random-effects model within a Bayesian framework, assuming a binomial likelihood and using WinBUGS 1.4.3 and R2WinBUGS package of R software 3.1.1 according to a pre-defined protocol (Item S1). We used non-informative priors with vague normal (mean, 0; variance, 100,000) and uniform (0 to 5) prior distributions for parameters such as means and standard deviations, respectively.\textsuperscript{11} For each analysis, we generated 200,000 simulations for each of the two sets of different initial values, and discarded the first 80,000 simulations as the burn-in period. Convergence was reached when Rhat, the potential scale reduction factor is close to 1 for each of the parameters using the Brooks–Gelman–Rubin statistic.\textsuperscript{23} We used the surface under the cumulative ranking (SUCRA) probabilities to rank the treatments.\textsuperscript{24}

Inconsistency refers to differences in effect estimates between direct and indirect comparisons, which could be assessed when three treatments are connected within a loop.\textsuperscript{25,26} For each closed loop, we estimated the absolute difference between the direct and indirect comparisons, which is termed inconsistency factor. Inconsistent loops were identified by a significant disagreement (inconsistency factor and its 95% CI that excludes 0) between direct and indirect evidence.\textsuperscript{25,27,28} As a whole, inconsistency was also assessed by the comparison between the consistency model and inconsistency model of the network meta-analysis using deviance information criterion (DIC). A lower value of the DIC suggests a more parsimonious model. If the trade-off between model fit and complexity favours the model with assumes
inconsistency, then the assumption of consistency is likely to be violated.\textsuperscript{12,29}

We carried out the following pre-specified sensitivity analyses: exclusion of trials with sample sizes less than 50 in order to reduce small study effect and publication bias; exclusion of trials with high-osmolar and unspecified CM types; and exclusion of data from patients with non-DM (\textit{Item S1}). Other analyses were post-hoc: exclusion of trials evaluating only patients with normal kidney function, published before 2004, with oral hydration and unspecified hydration agent.

Pre-specified multiple-treatments meta-regression and subgroup analyses were conducted by several major covariates, such as mean CM dose, mean age, baseline serum creatinine concentration, different CI-AKI definitions, and different radiologic procedures with CM (\textit{Item S1}). Post-hoc subgroup analysis was conducted by types of CM and different hydration agents.

The models used, the WinBUGS codes, and R routines for all results are presented in detail and exemplified in http://www.mtm.uoi.gr and http://www.nicedsu.org.uk. A short summary is supplied in \textit{Item S3}.

\textbf{Results}

The literature search yielded 4144 articles. We assessed the full text of 396 of these articles for eligibility, and eventually included 150 RCTs in the network meta-analysis (Figure 1, see details of included studies in \textit{Table S1}). CI-AKI was measured according to the difference between the baseline serum creatinine level and the level within 48 h-72h in 120 studies. In 30 trials, CI-AKI was defined according to different
points in time and measurements (e.g. eGFR, Ccr), or the determination method was not specified. Of the included RCTs, 104 trials included patients with impaired renal function, 37 trials included patients with normal or impaired renal function, and 9 trials included only patients with normal renal function. Participants were recruited at an average age of 67 years, and male participants accounted for 68% of the total population. A total of 11 types of CM were used, including iso-osmolar, low-osmolar, and high-osmolar media. The dosing regimens and types of CM used in the included trials are detailed in Table S1.

The methodological quality of the included trials was not high overall and varied substantially (Item S2, Figure S1, S2). The proportion of trials with a low risk of bias was 53% in terms of random sequence generation, 54% in terms of allocation concealment, 49% in terms of blinding of both participants and health care professionals, 59% in terms of blinding of outcome assessors, 48% in terms of attrition, and 35% in terms of reporting bias. With respect to conflicts of interest, about 50% of RCTs were funded by pharmaceutical industry and 51% reported author-industry financial relationships. In order to investigate reporting/published bias, we searched and found 21 protocols for 396 full-text reviewed articles. In studies without reporting the outcome of interest, we didn’t find any pre-planned CI-AKI outcome.

A total of 4,182 CI-AKI events were reported in 150 trials with 31,631 participants. Figure 2 shows all comparisons that were analysed in the network meta-analysis. The results of available direct comparisons are shown in Figure 3 and Table S2, and the
results of testing heterogeneity ($I^2$, $\tau^2$ and $Q$) within treatment strategies were showed in Table S2. We summarized the results of random-effects consistency network meta-analysis in Figure 3. The effects of individual treatment strategies compared with hydration on preventing CI-AKI are presented in Figure 4. Compared with hydration alone, high-dose statin plus NAC, high-dose statin, prostaglandin, theophylline, bicarbonate sodium plus NAC, vitamins and their analogues and NAC alone (all in combination with hydration) statistically significantly reduced the risk of CI-AKI (Figure 3 and Figure 4). In addition, high-dose statins were significantly more effective than low-dose statins (OR: 0.42; 95% CrI: 0.19 to 0.79), NAC (OR: 0.51; 95% CrI: 0.29 to 0.98) and bicarbonate sodium (OR: 0.49; 95% CrI: 0.23 to 0.86). Prostaglandin was significantly more effective than bicarbonate sodium (OR: 0.49; 95% CrI: 0.22 to 0.98). High-dose statin combined with NAC was statistically more effective than NAC (OR: 0.41; 95% CrI: 0.22 to 0.86), low-dose statins (OR: 0.28; 95% CrI: 0.12 to 0.99), bicarbonate sodium plus NAC (OR: 0.51; 95% CrI: 0.24 to 0.99) and bicarbonate sodium alone (OR: 0.35; 95% CrI: 0.18 to 0.79).

High-dose statin plus NAC (SUCRA: 0.90) and high-dose statin (SUCRA: 0.83) were most likely to be ranked the best or second best (Figure S3). They were followed by prostaglandins (SUCRA: 0.82) and theophyllines (SUCRA: 0.70). SUCRAs (range: 0.41 to 0.49) and rankings were similar for bicarbonate sodium plus NAC, vitamins and its analogues, natriuretic peptides, fenoldopam and NAC.

Hydration alone was ranked as the least effective treatment.

The DIC value was lowest in the random consistency model than in the other three
models, which indicated that the former was the preferred model with a better trade-off between model fit and complexity (Table S3). However, significant discrepancy between the direct and indirect comparisons was identified in two of the 13 loops (Figure S4). The two inconsistent loops consisted of (1) vitamins and its analogues vs. bicarbonate sodium plus NAC vs. hydration; and (2) vitamins and its analogues vs. bicarbonate sodium plus NAC vs. NAC. Further investigation was performed, but we were unable to identify possible sources of inconsistency. As the number of relevant studies in the inconsistent loops was small, the extent of inconsistency was not substantial enough to affect the overall results.

Treatments with high-dose statin plus NAC or high-dose statin were consistently associated with the lowest or second lowest incidence of CI-AKI in sensitivity analyses, meta-regression, and subgroup analyses (Table S4 and S5). A notable exception is that the effects of vitamins and its analogues became statistically non-significant compared with hydration in some sensitivity and subgroup analyses.

When the analysis included only DM participants (38 trials, 7984 patients and 826 events), credible intervals were wide and all ORs were no longer statistically significant due to the reduced sample size, although high-dose statin plus NAC and high-dose statin remained the first and the second ranking among all treatment strategies. None of the other sensitivity, meta-regression, or subgroup analyses led to important changes in the overall results (Table S4 and S5).

**Discussion**
Our study included 150 trials with more than 30,000 participants and a total of 4,182 CI-AKI events. The mixed treatment comparison of 12 treatment strategies for preventing CI-AKI confirmed that treatment with a high-dose statin alone or in combination with NAC (both in combination with hydration) during CM administration significantly reduced the risk of CI-AKI compared with hydration alone. Compared with other protective regimens, oral administration of high-dose statins is simple and convenient. These results indicate an opportunity to potentially simplify prevention strategies for CI-AKI. Our analysis also found a number of other strategies that appeared to be superior to hydration alone, including prostaglandins, theophylline, bicarbonate sodium plus NAC, vitamins and their analogues and NAC.

A recent comprehensive pairwise meta-analysis reported that the greatest reduction in CI-AKI was seen with NAC plus hydration and with statins plus NAC plus hydration in patients receiving CM.30 Our study simultaneously compared multiple treatment strategies using Bayesian network meta-analysis method, and found that patients using CM were most likely to benefit from high-dose statin. The results of the current study were similar to findings from previous primary studies31–34 and meta-analyses,6,35–37 which suggested that short-term prophylaxis with high-dose statins led to a significant reduction in the risk of CI-AKI. In contrast, the meta-analysis by Zhang T et al.38 found no significant reduction in the incidence of CI-AKI with statins treatment, as determined using the pooled estimate of the included trials. However, it should be noted that the meta-analysis by Zhang T et al incompletely include relevant randomized trials.39,40
Pre-existing renal dysfunction is an independent predictor of CI-AKI. Findings from some previous pairwise meta-analyses suggested that the use of statins may not be effective for patients with pre-existing chronic kidney disease (CKD). Our meta-regression analyses found that baseline serum creatinine concentration as a continuous covariate was not a statistically significant effect-modifier (regression coefficient: 0.09; 95% CrI: -1.86 to 1.90). Consistent with our results, the TRACK-D study involving almost 3,000 DM participants with mild-to-moderate CKD demonstrated a significant reduction in the relative risk of CI-AKI with rosuvastatin therapy.

Although the pathogenesis of CI-AKI is not completely understood, multiple mechanisms are probably involved, including direct toxicity of CM on the renal tubular epithelium, inflammatory reactions, oxidative stress, ischemic injury, and renal tubular obstruction. Statins may have multiple non-lipid-lowering effects, such as enhancement of endothelial nitric oxide production, anti-inflammatory and anti-oxidative actions, and apoptosis prevention. These pleiotropic effects of statins could mediate the reduction of CI-AKI risk after iodinated contrast administration. Furthermore, use of antioxidants (eg, vitamins and its analogues, NAC) might be an effective strategy to prevent CI-AKI, considering their roles in attenuating the oxidative damage from radiocontrast.

Apart from high-dose statins and high-dose statins plus NAC, prostaglandins had better effects than other treatment strategies, based on evidence from five trials that included a total of 943 participants and evaluated four classes of prostaglandins.
Adequate renal prostaglandin levels may counteract contrast-induced renal vasoconstriction and selective renal tubular epithelial cell toxicity.\textsuperscript{48} As a non-selective adenosine receptor antagonist, theophylline may help attenuate the vasoconstrictive tendencies observed after CM administration.\textsuperscript{49,50} A previous pairwise meta-analysis also showed that theophylline administration reduced the incidence of CI-AKI compared with the control group.\textsuperscript{51} Although pre-interventional theophylline administration might be helpful in patients with CM, the possibility of cardiovascular side-effects and the interactions with numerous drugs associated with theophylline should be recognized.\textsuperscript{52,53}

Many but not all studies reported that NAC has a protective effect on CI-AKI when administered before the onset of renal insult. Of the 11 previous meta-analyses published on this subject, seven found a net benefit of NAC in CI-AKI prevention. However, due to statistically significant heterogeneity and possible publication bias, the benefit of NAC might have been overestimated.\textsuperscript{54} With low the strength of evidence, Kidney Disease Improving Global Outcomes Clinical Practice Guideline for CI-AKI suggests the use of oral N-acetylcysteine plus hydration. Another meta-analysis found that a combination of NAC and sodium bicarbonate substantially reduced CI-AKI risk compared with NAC alone.\textsuperscript{55} However, we found that both sodium bicarbonate plus NAC and vitamins and their analogues were involved in significant inconsistent loops, and results for vitamins and their analogues were not robust in sensitivity and subgroup analyses.

This network meta-analysis provides a most comprehensive picture of the
likelihood of a range of treatments to prevent CI-AKI, and reports the results of mixed comparisons of multiple treatments that have been rarely compared in head to head trials. We also report the ranking probability for all 12 treatment agents. However, treatment rankings derived from network meta-analyses may have a substantial degree of imprecision, and the results in terms of treatment ranking should be interpreted with caution.

Our study has several limitations. First, the trial network could not include some treatment agents, such as Na/K citrate, allopurinol, statin plus alprostadil, that may be efficacious but were evaluated in only one or two small trials without a connection with other commonly used treatments. For many specific treatments, the number of patients and events in the available trials may not be sufficient to form a well-connected network for meta-analysis. We therefore combined drugs with the same types and similar mechanism of action and evaluated treatment effects of major drug classes. Second, many of the included studies showed low CI-AKI event rates or no events at all in one or both trial arms, and there was an imbalance in the distribution of participants among some of the treatment strategies. Consequently, the uncertainty in the analyses was increased, resulting in wide CrIs for several treatment comparisons. Third, the absence of patient-specific data, varying quality and design of the included studies are limitations common to all meta-analyses. To at least partly nullify the latter factors, we included only RCTs. Furthermore, the meta-regression based on trial-level covariates rather than individual patient data might bring the ecological fallacy. Fourth, we included only published studies in this analysis, and
reporting bias could not be ruled out because not all studies reported CI-AKI outcome, especially when CI-AKI events were not primary end points.

Further studies with head-to-head comparisons of statins at both high and low doses were needed to illuminate whether important differences exist in their abilities to reduce CI-AKI risk and whether dose matters. Prospective randomized trials should focus on relatively homogeneous patient populations, such as DM, or whether patients with different stages of CKD would benefit similarly or differently from peri-procedural statin therapy. Future studies are also needed to test effects of combinations of different strategies shown to be beneficial in this analysis, and to uncover possible mechanisms.

Our Bayesian network meta-analysis indicates the effects and superiority of using a high-dose statin plus hydration with or without NAC in patients undergoing diagnostic and/or interventional procedures requiring CM. The results should be interpreted with caution due to important data and methodological limitations.

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**Contributions:** Research idea and study design: LL, XS, XX, JL, HZ; data acquisition: XS, XX; data analysis/interpretation: LL, XS, XX, VP, FS; statistical analysis: LL, XS, XX, FS; supervision or mentorship: LL, JL, VP, HZ. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. LL take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

**References**


49. Katholi RE, Taylor GJ, McCann WP, et al. Nephrotoxicity from contrast media:


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**Figure 1: Summary of trial identification and selection**

**Figure 2: Network of treatment comparisons for the Bayesian network meta-analysis**
The size of the nodes is proportional to the number of patients randomized to receive the treatment. Directly comparable treatments are linked with a line, the width of which is proportional to the number of trials comparing the connected treatments.

NAC, N-acetylcysteine.

**Figure 3: Summary of the results from NMA (on the lower triangle) and traditional pairwise meta-analysis** (on the upper triangle)
On the lower triangle, the column-defining treatment is compared with the row-defining treatment, and odds ratios (ORs) lower than 1 favor the column-defining treatment. On the upper triangle, the row-defining treatment is compared with the column-defining treatment, and ORs lower than 1 favor the row-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold. The direct comparisons within two inconsistent loops are underlined.

BIC, Bicarbonate sodium; BIC+NAC, Bicarbonate sodium plus NAC; FEN, Fenoldopam; HST, High-dose statin; HST+NAC, High-dose statin plus NAC; HYD, Hydration; LST, Low-dose statin; NAC, N-acetylcysteine; NAP, Natriuretic peptide; PRO, Prostaglandin; THE, Theophylline; VIT, Vitamins and its analogues.

**Figure 4: Forest plot for efficacy of 11 active drugs compared with hydration**
Treatments are ranked according to their OR values (vs. hydration).

CrI, credible interval. SUCRA, surface under the cumulative ranking curve measure. NAC, N-acetylcysteine. OR, odds ratio.
Supplemental Material

Table S1: Description of included studies
ALA, alpha-lipoic acid; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CI-AKI, contrast-induced acute kidney injury; Crcl, Creatinine clearance rate; eGFR, estimated glomerular filtration rate; NA, no available; NAC, N-acetylcysteine; NaHCO₃, bicarbonate sodium; Scr, Serum creatinine.

Table S2: Meta-analytic results of traditional pairwise meta-analysis
Abbreviations: CI, confidence interval; N, number of trials; n, number of patients; NA, no available; NAC, N-acetylcysteine; OR, odds ratio, vs., versus.

Table S3: Evaluation of the model fit
For a binomial likelihood each trial arm contributes 1 independent data point. Dbar is considered as an absolute measure of fit, and is used to check formally whether a model’s fit is satisfactory. This is the posterior mean of the deviance under the current model minus the deviance for the saturated mode. We can then compare the value of Dbar to the number of independent data points to check if the model fit can be improved. Leverage (P₀) is considered an appropriate measure of the complexity of a model that reasonably describes the data. P₀ also is termed the effective number of parameters, and is calculated as the posterior mean of the residual deviance minus the deviance at the posterior mean of the fitted values. Deviance Information Criterion (DIC) is the sum of the posterior mean of the residual deviance and the P₀, and provides a measure of model fit that penalises model complexity – lower values of the DIC suggest a more parsimonious model. The DIC is particularly useful for comparing different parameter models for the same likelihood and data, for example fixed and random effects models or fixed effect models with and without covariates. As shown in above table, the random consistency model is clearly more parsimonious than the other three models.

Table S4: Results of sensitivity analyses
Data are odds ratio (95% CrI). All odds ratios use hydration as referenced agent. Heterogeneity was assessed using the posterior median between trial variance, τ². Significant results are in bold. CM, contrast media; CrI, credible interval; DM, Diabetes mellitus; SUCRA, surface under the cumulative ranking curve measure; NAC, N-acetylcysteine.
Table S5: Results of meta-regression and subgroup analyses
Data are odds ratio (95% CrI) after adjusting covariates: a. continuous variables include “Mean CM dose”, “Baseline scr concentration”, and “Mean age years”; b. categorical variables include “CM type (iso-, low- or high-osmolar)”, “Isotonic (0.9%) or hypotonic (0.45%) saline hydration”, “Different CI-AKI definitions (48h,72h or 120h)”, “Cardiovascular diagnostic/interventional procedures or enhanced CT or not specified radiologic procedure with CM”. All odds ratios use hydration as referenced agent. Heterogeneity was assessed using the posterior median between trial variance, $\tau^2$.
Significant results are in bold.
CM, contrast media; CrI, credible interval; CT, computed tomography; Scr, Serum creatinine; NAC, N-acetylcysteine.

Figure S1: Risk of bias summary: judgements from each study
The green symbols represent low risk of bias, the yellow symbols represent unclear risk of bias, and the red symbols represent high risk of bias. The figure was generated using Review Manager Version 5.0.16.

Figure S2: Risk of bias graph of included clinical trials
Each methodological quality item is presented as percentages across all included studies. The figure was generated using Review Manager Version 5.0.16.

Figure S3: Cumulative and non-cumulative SUCRA ranking curves
Treatment is ranked according to SUCRA. The SUCRA would be 1 when a treatment is certain to be the best and 0 when a treatment is certain to be the worst. Higher rank indicates greater benefit probability of preventing CI-AKI. SUCRA, surface under the cumulative ranking curve measure; NAC, N-acetylcysteine.

Figure S4: Assessment of inconsistency
We estimated inconsistency as the difference between direct and indirect estimates (called inconsistency factor, IF) and the corresponding 95% confidence intervals (CI) for IF in each closed loop. The following graphs show all closed triangular loops (loops formed by three treatments) in CI-AKI outcome network. Inconsistent loops are those that present IF with 95% CIs incompatible with zero. There are two inconsistent loops (1–11–9 = Vitamins and its analogues – Bicarbonate sodium plus NAC – Hydration; 1–11–3 = Vitamins and its analogues – Bicarbonate sodium plus NAC – NAC) out of 13 loops.
1 = Vitamins and its analogues, 2 = Natriuretic peptide, 3 = NAC, 4 = Prostaglandin, 5 = High-dose statin, 6 = Low-dose statin, 7 = Theophylline, 8 = Bicarbonate sodium, 9 = Hydration, 10 = Fenoldopam, 11 = Bicarbonate sodium plus NAC, 12 = High-dose statin plus NAC.

Item S1: Study protocol
Item S2: Statistical method
Item S3: Assessment domains of risk of bias
Item S4: PRISMA checklist
### Table S1  Description of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Number of patients</th>
<th>Men (%)</th>
<th>Mean age</th>
<th>CM Type</th>
<th>Volume of CM (mL)</th>
<th>Inclusion criteria of kidney function</th>
<th>Drug 1</th>
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<td>9/80</td>
<td>NA</td>
<td></td>
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<td>Miao</td>
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<td>330</td>
<td>77</td>
<td>79</td>
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<td>Scr&lt;3mg/dl</td>
<td>Alprostadil+Hydration</td>
<td>14/154</td>
<td>Placebo+hydration</td>
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<td>Non-industry</td>
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<tr>
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<td>50</td>
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<td>NAC+Hydration</td>
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<td>Placebo+hydration</td>
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<td>NA</td>
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<td>Stephen</td>
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<td>Placebo+hydration</td>
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<td>T2</td>
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<td>Pathology</td>
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<td>low-osmolar</td>
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<td>NAC+hydration</td>
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<td>Han et al.</td>
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<td>2014</td>
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<td>91</td>
<td>no limited kidney function</td>
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<td>49/126 NaHCO3+hydration 75/125 NaHCO3+NAC 72/124 hydration 61/125</td>
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<td>Kama et al.</td>
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<td>NA</td>
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<td>7/36 NaHCO3+hydration 4/36 hydration 5/35</td>
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<td>PRATO-ACS</td>
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<td>17/252 NAC+hydration 38/252</td>
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<tr>
<td>Li et al.</td>
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<td>eGFR&gt;30m/ min Prostaglandin E1+hydration</td>
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<td>9/81</td>
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<td>Manati et al.</td>
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<tr>
<td>PROMEC</td>
<td>2014</td>
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<td>Scr&gt;1.2mg/dl</td>
<td>NaHCO3</td>
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<td>Thayssen et al.</td>
<td>2014</td>
<td>715</td>
<td>77</td>
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<td>iodixanol</td>
<td>iso-osmolar</td>
<td>140</td>
<td>no dialysis</td>
<td>hydration</td>
<td>43/181 NAC+hydration 32/176 NaHCO3+hydration 33/181 NaHCO3+NAC 33/177</td>
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<tr>
<td>Yang et al.</td>
<td>2014</td>
<td>527</td>
<td>45</td>
<td>59</td>
<td>iohexol</td>
<td>low-osmolar</td>
<td>127</td>
<td>eGFR&gt;30m/ min</td>
<td>hydration</td>
<td>5/161 NAC+hydration 7/157 NaHCO3 8/159 NaHCO3+NAC 8/150</td>
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<tr>
<td>Fahmy et al.</td>
<td>2014</td>
<td>200</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Rosuvastatin 20mg+hydration</td>
<td>15/100 placebo+hydration 38/100</td>
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<tr>
<td>Yeganekhah et al.</td>
<td>2014</td>
<td>78</td>
<td>78</td>
<td>59</td>
<td>iohexol</td>
<td>low-osmolar</td>
<td>44</td>
<td>Scr&lt;4mg/dl</td>
<td>NaHCO3+hydration</td>
<td>7/50 NAC+hydration 6/50 hydration 7/50</td>
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<tr>
<td>Abaci et al.</td>
<td>2015</td>
<td>208</td>
<td>71</td>
<td>68</td>
<td>ioversol</td>
<td>low-osmolar</td>
<td>129</td>
<td>eGFR 30-60m/ min</td>
<td>Rosuvastatin 40mg+hydration</td>
<td>6/103 hydration 9/105</td>
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<td></td>
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<tr>
<td>Arabmomeh et al.</td>
<td>2015</td>
<td>62</td>
<td>43</td>
<td>62</td>
<td>iodixanol</td>
<td>low-osmolar</td>
<td>136</td>
<td>normal kidney function</td>
<td>theophylline+hydration</td>
<td>6/30 NAC+hydration 7/32</td>
<td></td>
<td></td>
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<tr>
<td>Bidram et al.</td>
<td>2015</td>
<td>200</td>
<td>91</td>
<td>60</td>
<td>iodixanol</td>
<td>iso-osmolar</td>
<td>35</td>
<td>eGFR&gt;60m/ min</td>
<td>atorvastatin 80mg+hydration</td>
<td>1/100 placebo+hydration 2/100</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CONTRAS T et al.</td>
<td>2015</td>
<td>453</td>
<td>76</td>
<td>68</td>
<td>iohexol or iopamidol or ioversol or ipromide</td>
<td>low-osmolar</td>
<td>116</td>
<td>eGFR 15-60m/ min</td>
<td>NAC+hydration</td>
<td>10/153 NaHCO3 19/149 NAC+NaHCO3 16/151</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Galal et al.</td>
<td>2015</td>
<td>80</td>
<td>64</td>
<td>56</td>
<td>NA</td>
<td>low-osmolar</td>
<td>241</td>
<td>eGFR 60-90m/ min</td>
<td>Atorvastatin 80mg+hydration</td>
<td>5/40 Atorvastatin 10mg+hydration 7/40</td>
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</table>

No funding supported
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Indication</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jo</td>
<td>2015</td>
<td>218</td>
<td>85</td>
<td>59</td>
<td>NA</td>
<td>Atorvastatin 80mg+hydration</td>
</tr>
<tr>
<td>Shehata</td>
<td>2015</td>
<td>130</td>
<td>62</td>
<td>56</td>
<td>low-osmolar</td>
<td>atorvastatin 80mg+hydration+NAC</td>
</tr>
<tr>
<td>BOSS</td>
<td>2015</td>
<td>391</td>
<td>58</td>
<td>72</td>
<td>NA</td>
<td>NaHCO3</td>
</tr>
<tr>
<td>Rezaei</td>
<td>2016</td>
<td>298</td>
<td>69</td>
<td>67</td>
<td>low-osmolar</td>
<td>Vitamin E+hydration</td>
</tr>
</tbody>
</table>

ALA, alpha-lipoic acid; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CI-AKI, contrast-induced acute kidney injury; Crcl, Creatinine clearance rate; eGFR, estimated glomerular filtration rate; NA, no available; NAC, N-acetylcysteine; NaHCO3, bicarbonate sodium; Scr, Serum creatinine.
Reference


45. Boscheri A, Weinbrenner C, Botzek B, Reynen K, Kuhlisch E, Strasser RH. Failure of ascorbic acid to prevent contrast-


74. Tamura A, Goto Y, Miyamoto K, et al. Efficacy of single-bolus administration of sodium bicarbonate to prevent contrast-


84. Malhis M, Al-Bitar S, Al-Deen Zaiat K. The role of theophylline in prevention of radiocontrast media-induced


intervention or arteriography (the PREVENT Trial). *Am J Cardiol.* 2011; 107: 1447-1452.


134. Leoncini M, Toso A, Maioli M, Tropeano F, Villani S, Bellandi F. Early high-dose rosuvastatin for contrast-induced nephropathy prevention in acute coronary syndrome: Results from the PRATO-ACS Study (Protective Effect of Rosuvastatin


Table S2. Meta-analytic results of traditional pairwise meta-analysis

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>N</th>
<th>n</th>
<th>$\tau^2$</th>
<th>I²% (95%CI)</th>
<th>Q</th>
<th>OR (95%CI)$^b$ from traditional pairwise meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamins and its analogues vs. hydration</td>
<td>13</td>
<td>2149</td>
<td>0</td>
<td>0(0.58)</td>
<td>10.19</td>
<td>0.49(0.33,0.70)</td>
</tr>
<tr>
<td>Vitamins and its analogues vs. NAC</td>
<td>5</td>
<td>821</td>
<td>0</td>
<td>0(0.85)</td>
<td>2.58</td>
<td>0.80(0.17,2.29)</td>
</tr>
<tr>
<td>Vitamins and its analogues vs. bicarbonate sodium+NAC</td>
<td>1</td>
<td>215</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>6.70(1.46,30.68)</td>
</tr>
<tr>
<td>Natriuretic peptide vs. hydration</td>
<td>4</td>
<td>762</td>
<td>0.5</td>
<td>68(6,89)</td>
<td>9.3</td>
<td>0.60(0.07,4.78)</td>
</tr>
<tr>
<td>NAC vs. theophylline</td>
<td>3</td>
<td>152</td>
<td>0.67</td>
<td>29(0.93)</td>
<td>2.83</td>
<td>1.05(0.003,252)</td>
</tr>
<tr>
<td>NAC vs. bicarbonate sodium</td>
<td>11</td>
<td>1959</td>
<td>0.26</td>
<td>53(8,76)</td>
<td>21.45</td>
<td>0.77(0.47,1.22)</td>
</tr>
<tr>
<td>NAC vs. hydration</td>
<td>70</td>
<td>12128</td>
<td>0.17</td>
<td>36(14,52)</td>
<td>104.68</td>
<td>0.74(0.62,0.88)</td>
</tr>
<tr>
<td>NAC vs. fenoldopam</td>
<td>2</td>
<td>276</td>
<td>0</td>
<td>0$^c$</td>
<td>0.55</td>
<td>0.32(0.006,147.8)</td>
</tr>
<tr>
<td>NAC vs. bicarbonate sodium+NAC</td>
<td>12</td>
<td>2792</td>
<td>0.63</td>
<td>65(35,81)</td>
<td>31.53</td>
<td>1.19(0.61,2.14)</td>
</tr>
<tr>
<td>NAC vs. high-dose statin+NAC</td>
<td>6</td>
<td>1228</td>
<td>0.06</td>
<td>23(0.68)</td>
<td>5.21</td>
<td>2.57(0.94,4.87)</td>
</tr>
<tr>
<td>Prostaglandin vs. hydration</td>
<td>5</td>
<td>943</td>
<td>0</td>
<td>0(0.79)</td>
<td>1.87</td>
<td>0.35(0.17,0.65)</td>
</tr>
<tr>
<td>High-dose statin vs. low-dose statin</td>
<td>5</td>
<td>806</td>
<td>0</td>
<td>0(0.79)</td>
<td>2.21</td>
<td>0.69(0.08,0.78)</td>
</tr>
<tr>
<td>High-dose statin vs. hydration</td>
<td>7</td>
<td>1437</td>
<td>0.1</td>
<td>21(0,64)</td>
<td>7.59</td>
<td>0.38(0.18,0.71)</td>
</tr>
<tr>
<td>Low-dose statin vs. hydration</td>
<td>1</td>
<td>2998</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.58(0.38,0.89)</td>
</tr>
<tr>
<td>Theophylline vs. bicarbonate sodium</td>
<td>1</td>
<td>280</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.19(0.04,0.85)</td>
</tr>
<tr>
<td>Theophylline vs. hydration</td>
<td>9</td>
<td>739</td>
<td>0.39</td>
<td>32(0.69)</td>
<td>11.73</td>
<td>0.55(0.18,1.21)</td>
</tr>
<tr>
<td>Bicarbonate sodium vs. hydration</td>
<td>28</td>
<td>5561</td>
<td>0.66</td>
<td>60(40,74)</td>
<td>68.35</td>
<td>0.68(0.46,0.95)</td>
</tr>
<tr>
<td>Bicarbonate sodium vs. bicarbonate sodium+NAC</td>
<td>8</td>
<td>1598</td>
<td>0.13</td>
<td>25(0,66)</td>
<td>9.28</td>
<td>1.21(0.70,2.04)</td>
</tr>
<tr>
<td>Fenoldopam vs. hydration</td>
<td>2</td>
<td>328</td>
<td>0.32</td>
<td>55$^c$</td>
<td>2.26</td>
<td>0.76(0.009,516.7)</td>
</tr>
<tr>
<td>Bicarbonate sodium+N AC vs. hydration</td>
<td>6</td>
<td>1194</td>
<td>0.06</td>
<td>1(0,75)</td>
<td>5.07</td>
<td>1.21(0.70,2.04)</td>
</tr>
<tr>
<td>High-dose statin+NAC vs. bicarbonate sodium+NAC</td>
<td>1</td>
<td>410</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.45(0.20,1.23)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; N, number of trials; n, number of patients; NA, no available; NAC, N-acetylcysteine; OR, odds ratio, vs., versus.

$^a$ $\tau^2$ represents between-study heterogeneity characterized by standard deviation.

$^b$ the meta-regression based on empirical Bayes method was used to calculate ORs and 95CIs. ORs are lower than 1 favor the former treatment of every comparison.
Table S3. Evaluation of the model fit

<table>
<thead>
<tr>
<th>Model assumption</th>
<th>Dbar</th>
<th>Pd</th>
<th># of data points</th>
<th>DIC</th>
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<tbody>
<tr>
<td>Random consistency</td>
<td>338</td>
<td>232</td>
<td>322</td>
<td>570</td>
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<tr>
<td>Random inconsistency</td>
<td>343</td>
<td>236</td>
<td>322</td>
<td>579</td>
</tr>
<tr>
<td>Fixed consistency</td>
<td>629</td>
<td>156</td>
<td>322</td>
<td>785</td>
</tr>
<tr>
<td>Fixed inconsistency</td>
<td>502</td>
<td>168</td>
<td>322</td>
<td>630</td>
</tr>
</tbody>
</table>

For a binomial likelihood each trial arm contributes 1 independent data point.

Dbar is considered as an absolute measure of fit, and is used to check formally whether a model’s fit is satisfactory. This is the posterior mean of the deviance under the current model minus the deviance for the saturated mode. We can then compare the value of Dbar to the number of independent data points to check if the model fit can be improved.

Leverage (P_D) is considered an appropriate measure of the complexity of a model that reasonably describes the data. P_D also is termed the effective number of parameters, and is calculated as the posterior mean of the residual deviance minus the deviance at the posterior mean of the fitted values.

Deviance Information Criterion (DIC) is the sum of the posterior mean of the residual deviance and the P_D, and provides a measure of model fit that penalises model complexity – lower values of the DIC suggest a more parsimonious model. The DIC is particularly useful for comparing different parameter models for the same likelihood and data, for example fixed and random effects models or fixed effect models with and without covariates. As shown in above table, the random consistency model is clearly more parsimonious than the other three models.
Table S4. Results of sensitivity analyses

<table>
<thead>
<tr>
<th>Treatment strategies</th>
<th>Standard analysis</th>
<th>Excluding 13 trials with sample size less than 50</th>
<th>Excluding 18 trials with high-osmolar and unspecified CM type</th>
<th>Excluding 14 trials with oral hydration and unspecified hydration agent</th>
<th>Excluding 9 trials evaluated only patients with normal kidney function</th>
<th>Excluding data for non-DM patients</th>
<th>Excluding 24 trials published before 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose statin+NAC</td>
<td>0.31 (0.14, 0.60)</td>
<td>0.32 (0.15, 0.58)</td>
<td>0.32 (0.14, 0.64)</td>
<td>0.38 (0.15, 0.83)</td>
<td>0.32 (0.14, 0.66)</td>
<td>0.24 (0.07, 1.27)</td>
<td>0.33 (0.16, 0.60)</td>
</tr>
<tr>
<td>High-dose statin</td>
<td>0.37 (0.19, 0.64)</td>
<td>0.38 (0.21, 0.64)</td>
<td>0.39 (0.21, 0.68)</td>
<td>0.35 (0.17, 0.62)</td>
<td>0.42 (0.20, 0.72)</td>
<td>0.47 (0.11, 1.33)</td>
<td>0.38 (0.21, 0.62)</td>
</tr>
<tr>
<td>Prostaglandin</td>
<td>0.37 (0.17, 0.72)</td>
<td>0.37 (0.17, 0.68)</td>
<td>0.43 (0.16, 0.86)</td>
<td>0.40 (0.17, 0.74)</td>
<td>0.45 (0.21, 0.87)</td>
<td>-</td>
<td>0.42 (0.16, 0.88)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>0.48 (0.26, 0.82)</td>
<td>0.46 (0.24, 0.82)</td>
<td>0.46 (0.26, 0.75)</td>
<td>0.55 (0.29, 0.93)</td>
<td>0.48 (0.23, 0.85)</td>
<td>0.77 (0.01, 4.69)</td>
<td>0.60 (0.27, 1.14)</td>
</tr>
<tr>
<td>Bicarbonate sodium+NAC</td>
<td>0.62 (0.40, 0.88)</td>
<td>0.57 (0.38, 0.80)</td>
<td>0.47 (0.30, 0.69)</td>
<td>0.54 (0.36, 0.77)</td>
<td>0.55 (0.37, 0.79)</td>
<td>1.14 (0.46, 2.42)</td>
<td>0.56 (0.37, 0.82)</td>
</tr>
<tr>
<td>Vitamins and its analogues</td>
<td>0.64 (0.41, 0.95)</td>
<td>0.64 (0.42, 0.96)</td>
<td>0.58 (0.38, 0.87)</td>
<td>0.63 (0.41, 0.95)</td>
<td>0.62 (0.38, 0.93)</td>
<td>0.87 (0.43, 1.57)</td>
<td>0.75 (0.48, 1.13)</td>
</tr>
<tr>
<td>NAC</td>
<td>0.67 (0.54, 0.81)</td>
<td>0.71 (0.58, 0.87)</td>
<td>0.64 (0.52, 0.77)</td>
<td>0.67 (0.54, 0.81)</td>
<td>0.66 (0.54, 0.81)</td>
<td>0.81 (0.54, 1.14)</td>
<td>0.73 (0.59, 0.88)</td>
</tr>
<tr>
<td>Natriuretic peptide</td>
<td>0.69 (0.31, 1.37)</td>
<td>0.71 (0.31, 1.40)</td>
<td>0.70 (0.32, 1.34)</td>
<td>0.71 (0.30, 1.31)</td>
<td>0.71 (0.31, 1.35)</td>
<td>1.91 (0.45, 5.71)</td>
<td>0.62 (0.27, 1.30)</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>0.70 (0.32, 1.36)</td>
<td>1.69 (0.68, 3.44)</td>
<td>1.22 (0.54, 2.48)</td>
<td>1.26 (0.57, 2.44)</td>
<td>1.26 (0.55, 2.52)</td>
<td>0.95 (0.41, 1.85)</td>
<td>2.53 (0.69, 7.05)</td>
</tr>
<tr>
<td>Bicarbonate sodium</td>
<td>0.78 (0.59, 1.01)</td>
<td>0.79 (0.60, 1.00)</td>
<td>0.66 (0.49, 0.84)</td>
<td>0.77 (0.58, 0.99)</td>
<td>0.78 (0.59, 1.01)</td>
<td>1.31 (0.67, 2.38)</td>
<td>0.78 (0.59, 0.99)</td>
</tr>
<tr>
<td>Low-dose statin</td>
<td>0.98 (0.41, 2.07)</td>
<td>0.96 (0.44, 1.90)</td>
<td>0.89 (0.39, 1.72)</td>
<td>0.74 (0.30, 1.52)</td>
<td>1.04 (0.41, 2.11)</td>
<td>0.65 (0.20, 1.52)</td>
<td>0.95 (0.42, 1.85)</td>
</tr>
<tr>
<td>Hydration</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>0.33 (0.21, 0.54)</td>
<td>0.35 (0.19, 0.56)</td>
<td>0.30 (0.16, 0.49)</td>
<td>0.34 (0.19, 0.55)</td>
<td>0.35 (0.19, 0.54)</td>
<td>0.15 (0.00, 0.71)</td>
<td>0.29 (0.15, 0.50)</td>
</tr>
<tr>
<td>DIC</td>
<td>570</td>
<td>521</td>
<td>500</td>
<td>522</td>
<td>541</td>
<td>142</td>
<td>480</td>
</tr>
<tr>
<td>Number of trials</td>
<td>150</td>
<td>137</td>
<td>132</td>
<td>125</td>
<td>141</td>
<td>38</td>
<td>126</td>
</tr>
<tr>
<td>Heterogeneity change</td>
<td>rise 6%</td>
<td>drop 9%</td>
<td>rise 3%</td>
<td>rise 6%</td>
<td>drop 55%</td>
<td>drop 12%</td>
<td></td>
</tr>
</tbody>
</table>

Data are odds ratio (95% CrI). All odds ratios use hydration as referenced agent. Heterogeneity was assessed using the posterior median between trial variance, \( I^2 \). Significant results are in bold. CM, contrast media; CrI, credible interval; DM, Diabetes mellitus; SUCRA, surface under the cumulative ranking curve measure; NAC, N-acetylcysteine;
### Table S5. Results of meta-regression and subgroup analyses

<table>
<thead>
<tr>
<th>Treatment strategies</th>
<th>Standard analysis</th>
<th>Mean CM dose</th>
<th>Baseline Scr concentration</th>
<th>Mean age years</th>
<th>CM type (iso-, low- or high-osmolar)</th>
<th>Isotonic (0.9%) or hypotonic (0.45%) saline hydration</th>
<th>Different CI-AKI definitions (48h, 72h or 120h)</th>
<th>Cardiovascular diagnostic/interventional procedures or enhanced CT or not specified radiologic procedure with CM</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose statin+NAC</td>
<td>0.31(0.14,0.60)</td>
<td>0.35(0.14,0.69)</td>
<td>0.29(0.13,0.55)</td>
<td>0.35(0.15,0.72)</td>
<td>0.33(0.14,0.65)</td>
<td>0.40(0.15,0.86)</td>
<td>0.33(0.14,0.66)</td>
<td>0.29(0.13,0.54)</td>
</tr>
<tr>
<td>High-dose statin</td>
<td>0.37(0.19,0.64)</td>
<td>0.36(0.15,0.76)</td>
<td>0.34(0.16,0.64)</td>
<td>0.35(0.17,0.68)</td>
<td>0.44(0.21,0.80)</td>
<td>0.39(0.17,0.75)</td>
<td>0.36(0.17,0.68)</td>
<td>0.33(0.17,0.58)</td>
</tr>
<tr>
<td>Prostaglandin</td>
<td>0.37(0.17,0.72)</td>
<td>0.40(0.14,0.89)</td>
<td>0.38(0.17,0.74)</td>
<td>0.37(0.17,0.76)</td>
<td>0.37(0.14,0.70)</td>
<td>0.43(0.19,0.82)</td>
<td>0.35(0.15,0.68)</td>
<td>0.47(0.20,0.92)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>0.48(0.26,0.82)</td>
<td>0.46(0.24,0.84)</td>
<td>0.47(0.25,0.79)</td>
<td>0.52(0.28,0.90)</td>
<td>0.48(0.25,0.84)</td>
<td>0.59(0.31,0.99)</td>
<td>0.45(0.24,0.77)</td>
<td>0.46(0.25,0.77)</td>
</tr>
<tr>
<td>Bicarbonate sodium+NAC</td>
<td>0.62(0.40,0.88)</td>
<td>0.54(0.35,0.80)</td>
<td>0.51(0.33,0.73)</td>
<td>0.55(0.37,0.79)</td>
<td>0.52(0.34,0.75)</td>
<td>0.57(0.36,0.84)</td>
<td>0.45(0.29,0.69)</td>
<td>0.52(0.34,0.75)</td>
</tr>
<tr>
<td>Vitamins and its analogues</td>
<td>0.64(0.41,0.95)</td>
<td>0.62(0.39,0.97)</td>
<td>0.63(0.39,0.96)</td>
<td>0.57(0.32,0.90)</td>
<td>0.88(0.41,1.67)</td>
<td>0.66(0.43,0.97)</td>
<td>0.70(0.45,1.03)</td>
<td>0.72(0.48,1.02)</td>
</tr>
<tr>
<td>NAC</td>
<td>0.67(0.54,0.81)</td>
<td>0.66(0.52,0.81)</td>
<td>0.66(0.52,0.82)</td>
<td>0.67(0.54,0.83)</td>
<td>0.65(0.53,0.79)</td>
<td>0.70(0.56,0.89)</td>
<td>0.67(0.53,0.82)</td>
<td>0.64(0.51,0.77)</td>
</tr>
<tr>
<td>Natriuretic peptide</td>
<td>0.69(0.31,1.37)</td>
<td>0.71(0.30,1.40)</td>
<td>0.71(0.31,1.35)</td>
<td>0.71(0.33,1.42)</td>
<td>0.70(0.30,1.45)</td>
<td>0.75(0.33,1.51)</td>
<td>0.91(0.33,1.88)</td>
<td>0.66(0.30,1.27)</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>0.70(0.32,1.36)</td>
<td>1.25(0.47,2.47)</td>
<td>1.25(0.54,2.47)</td>
<td>1.27(0.56,2.49)</td>
<td>1.25(0.53,2.39)</td>
<td>1.43(0.57,2.94)</td>
<td>1.21(0.52,2.35)</td>
<td>1.18(0.52,2.35)</td>
</tr>
<tr>
<td>Bicarbonate sodium</td>
<td>0.78(0.59,1.01)</td>
<td>0.78(0.59,1.02)</td>
<td>0.77(0.58,0.99)</td>
<td>0.78(0.60,1.01)</td>
<td>0.67(0.49,0.88)</td>
<td>0.79(0.59,1.04)</td>
<td>0.75(0.55,1.04)</td>
<td>0.74(0.55,0.96)</td>
</tr>
<tr>
<td>Low-dose statin</td>
<td>0.98(0.41,2.07)</td>
<td>0.92(0.33,2.10)</td>
<td>0.91(0.37,1.92)</td>
<td>0.94(0.32,2.18)</td>
<td>1.00(0.38,2.50)</td>
<td>0.79(0.31,1.65)</td>
<td>0.91(0.36,1.90)</td>
<td>0.83(0.34,1.68)</td>
</tr>
<tr>
<td>Hydration</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>0.33(0.21,0.54)</td>
<td>0.38(0.21,0.60)</td>
<td>0.34(0.19,0.56)</td>
<td>0.33(0.19,0.54)</td>
<td>0.33(0.19,0.54)</td>
<td>0.33(0.19,0.54)</td>
<td>0.33(0.20,0.55)</td>
<td>0.33(0.20,0.55)</td>
</tr>
<tr>
<td>B coefficient</td>
<td>0.001(-0.008,0.007)</td>
<td>-0.27(-2.04,1.48)</td>
<td>-0.05(-0.17,0.07)</td>
<td>0.45(-0.21,1.18)</td>
<td>-0.21(-0.58,0.19)</td>
<td>0.09(-0.19,0.35)</td>
<td>0.09(-0.10,0.28)</td>
<td>0.09(-0.10,0.28)</td>
</tr>
<tr>
<td>DIC</td>
<td>570</td>
<td>502</td>
<td>534</td>
<td>530</td>
<td>519</td>
<td>517</td>
<td>501</td>
<td>571</td>
</tr>
<tr>
<td>Heterogeneity change</td>
<td>rise 15%</td>
<td>rise 3%</td>
<td>0%</td>
<td>drop 9%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Data are odds ratio (95% CrI) after adjusting covariates: a. continuous variables include “Mean CM dose”, “Baseline scr concentration”, and “Mean age years”; b. categorical variables include “CM type (iso-, low- or high-osmolar)”, “Isotonic (0.9%) or hypotonic (0.45%) saline hydration”, “Different CI-AKI definitions (48h, 72h or 120h)”, “Cardiovascular diagnostic/interventional procedures or enhanced CT or not specified radiologic procedure with CM”. All odds ratios use
hydration as referenced agent. Heterogeneity was assessed using the posterior median between trial variance, $\tau^2$. Significant results are in bold. CM, contrast media; CrI, credible interval; CT, computed tomography; Scr, Serum creatinine; NAC, N-acetylcysteine.
Figure S2

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Pharmaceutical industry funding
- Author-industry financial ties and/or employment

Legend:
- Green: Yes (low risk of bias)
- Yellow: Unclear
- Red: No (high risk of bias)
Figure S3
Cumulative SUCRA ranking curves

Non-cumulative ranking curves
Item S1. Study protocol:

PROTOCOL

First drafted in October 2014
Modified in January 2015

Comparative Effectiveness of 12 Treatment Strategies in Preventing Contrast-Induced Acute Kidney Injury: A Systematic Review and Bayesian Network Meta-analysis

Xiaole Su, Xinfang Xie, Lijun Liu, Jicheng Lv, Fujian Song, Perkovic Vlado and Hong Zhang
Objectives:
Integrate the available evidence to compare various types of pharmacological strategies when used in patients undergoing diagnostic and/or interventional procedures with contrast media(CM) and create hierarchies of the comparative efficacy of active drug treatments on preventing contrast-induced acute kidney injury (CI-AKI).

Background
Acute injury in renal function induced by CM is generally mild and transient but can result in lasting renal dysfunction and the need for renal replacement therapy. CI-AKI is a leading cause of new onset kidney injury in hospitalized patients (1, 2). It is associated with significantly increased in-hospital morbidity and mortality, acceleration of chronic kidney disease, and increased costs of medical care (3). There have been a large number of pharmacological strategies to prevent CI-AKI so far, such as N-acetylcysteine (NAC), theophylline, fenoldopam, dopamine, iloprost, statins, bicarbonate sodium, ascorbic acid (vitamin C), vitamin E and. The question of which treatment strategies should be preferred for the prevention of CI-AKI is controversial, and traditional meta-analyses are hindered by heterogeneity across trials and the lack of trials direct comparing different treatment agents. We will undertake a network meta-analysis, which accounts for both direct and indirect comparisons to assess the efficacy of treatments on preventing CI-AKI.

Research Plan:
A) Methods of the Review
We will conduct a Bayesian-framework, multiple-treatments meta-analysis (which uses
both direct and indirect comparisons) of randomized controlled trials (RCTs) (4).

**B) Data Sources:**

Relevant RCTs will be identified by computerized searches from the following data sources without language restriction:

1) MEDLINE OVID SP (from 1947 through October 2014);

2) EMBASE (from 1966 through October 2014);

3) The Cochrane Central Register of Controlled Trials (no date restriction);

4) Reference lists in nephrology textbooks, review articles, and relevant trials were also searched.

**C) Study Selection:**

**Types of Studies:**

- **Inclusion criteria:**

  We will include RCTs compared two or more of treatment groups received: NAC, theophylline (aminophylline), fenoldopam, iloprost, alprostadil, prostaglandin E1, statins, statins plus NAC, bicarbonate sodium, bicarbonate sodium plus NAC, ascorbic acid, vitamin E, tocopherol, alpha-lipoic acid, atrial natriuretic peptide, B-type natriuretic peptide, carperitide and hydration or placebo plus hydration. All above active drug treatments were based on hydration. All participants underwent diagnostic and/or interventional procedures with CM.

- **Exclusion criteria:**

  Trials contained only one or none of the above strategies.

**Types of Participants:**
Inclusion criteria:

Adult patients (age $\geq 18$ years) underwent diagnostic and/or interventional procedures with CM.

Exclusion criteria: None

**Type of Intervention:**

- Treatment groups:
  - N-acetylcysteine, theophylline (aminophylline), fenoldopam, iloprost, alprostadil, prostaglandin E1, statins, statins plus NAC, bicarbonate sodium, bicarbonate sodium plus NAC, ascorbic acid, vitamin E or its analogues (tocopherol), alpha-lipoic acid, atrial natriuretic peptide, B-type natriuretic peptide, carperitide and hydration or placebo plus hydration;
  - Compared two or more of the above mentioned treatment agents;
  - All above active drug treatments were based on hydration.

**Type of Outcome Measures:**

- Primary Outcome
  - The occurrence of CI-AKI, defined as an absolute increase in baseline serum creatinine greater than 44.2 $\mu$mol/L (0.5 mg/dL) or a relative increase greater than 25% within typically 48-72 h after contrast injection. If 48-72 h data were not available, we used data within 5 days (the data point closest to 48-72 h was given preference).

- Secondary Outcome
  - None

**D) Assess Study Quality:**
We will use the Cochrane risk of bias method to appraise study quality on the seven domains (low, unclear, or high bias for sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias) (5).

E) Statistical analysis

We will use Stata 12.0 to perform the traditional pairwise meta-analysis. Bayesian network meta-analysis will be done with WinBUGS version 1.4.3 and the R2WinBUGS package of R software 3.1.1. Clinical outcome analyses were compared by odds ratios (ORs) and 95% credible intervals (CrIs) using a Bayesian hierarchical random-effects model. Model fit will be assessed by comparing deviance information criterion (DIC). We will use the surface under the cumulative ranking (SUCRA) probabilities to rank the treatments (6). We will estimate the absolute difference between direct and indirect estimates in each closed loop. A significant (95% CrI that excludes 0) disagreement between direct and indirect evidence will indicate Inconsistent loops (7,8).

We will do multiple-treatments meta-regression with the following covariates: mean age, mean CM dose, and baseline serum creatinine concentration (7). Subgroup analyses will be performed by comparing with trials using with different CI-AKI definitions, and comparing with trials of cardiovascular diagnostic/interventional procedures and CT examination (7). Sensitivity analyses will be conducted by only including of trials of DM patients and by excluding of trials with small sample size and trails of high-osmolar CM used.

F) The Search Strategy:
1) MEDLINE OVID SP

1. exp Acute Kidney Injury/

2. exp renal failure/

3. (kidney disease* or renal disease* or renal failure or kidney failure or acute kidney or acute renal or nephrotoxic or nephropathy).mp.

4. (impair or injury or damage or reduce).mp. and (renal or kidney).mp.

5. 1 or 2 or 3 or 4

6. (contrast-induced or contrast-associated).mp.

7. (contrast or radiocontrast or iopamidol or iodine or ioxaglic acid or iodine compounds).mp.

8. (iohexol or urography or tomography or X ray computed or diatrizoate).mp.

9. 6 or 7 or 8

10. randomized controlled trial.pt.

11. controlled clinical trial.pt.

12. randomized.ab.

13. placebo. ab.

14. clinical trials as topic.sh

15. randomly.ab.

16. trial.ti.

17. 10 or 11 or 12 or 13 or 14 or 15 or 16

18. animals.sh. not (humans.sh. and animals.sh.)

19. 17 not 18
20. 5 and 9 and 19

2) EMBASE

#1 'Acute Kidney Injury'/exp

#2 'renal failure'/exp

#3 ‘kidney disease’ or ‘renal disease’ or ‘renal failure’ or ‘kidney failure’ or ‘acute kidney’ or ‘acute renal’ or nephrotoxic or nephropathy

#4 (impair or injury or damage or reduce) and (renal or kidney)

#5 #1 OR #2 OR #3 OR #4

#6 ‘contrast-induced’ or ‘contrast-associated’

#7 contrast or radiocontrast or iopamidol or iodine or ‘ioxaglic acid’ or ‘iodine compound’

#8 iohexol or urography or tomography or ‘X ray computed’ or diatrizoate

#9 #6 OR #7 OR #8

#10 random$ OR blind$ OR placebo OR 'meta analysis'

#11 #5 AND #9 AND #10

3) CENTRAL

#1 MeSH descriptor: [Acute Kidney Injury] explode all trees

#2 MeSH descriptor: [renal failure] explode all trees

#3 kidney disease* or renal disease* or renal failure or kidney failure or acute kidney or acute renal or nephrotoxic or nephropathy
4) Reference lists of nephrology textbooks, review articles, and relevant trials were also searched.

Reference


**Item S2. Assessment domains of risk of bias**

We assessed risk of bias for sequence generation, allocation concealment, blinding, selective reporting, incomplete outcome data and other sources of bias, and determined overall risk of bias based on predefined rules, utilizing the Cochrane Collaboration risk of bias tool.¹

**Sequence generation  (Selection bias)**

- Low risk of bias, if randomization was generated by a computer, or a table of random numbers.
- High risk of bias, if method of randomization was inadequate (i.e. "quasi-randomized").
- Unclear risk of bias, if method of randomization was not described.

**Allocation concealment (Selection bias)**

- Low risk of bias, if the method of allocation involved a central independent unit or consecutively numbered sealed envelopes.
- High risk of bias, if allocation sequence was known to the investigators or conducted with an inadequate method.
- Unclear risk of bias, if the method of allocation concealment was not described.

**Blinding of participants and personnel (Performance bias)**

- Low risk of bias, if the study was of a double-blind design.
- High risk of bias, if the study was open-label.
- Unclear risk of bias, if there was insufficient information to determine whether the study was double-blind or open-label.
Blinding of outcome assessment (Detection bias)

- Low risk of bias, if the outcome assessment was blind.
- High risk of bias, if the outcome assessment was open.
- Unclear risk of bias, if there was insufficient information to determine whether the outcome assessment was blind or open.

Selective outcome reporting (Detection bias)

- Low risk of bias, if the specific outcome was reported adequately for all treatment arms.
- High risk of bias, if the specific outcome was reported with inadequate detail for the data to be included in a meta-analysis or if it was reported only for a subset of the randomized population.
- Unclear risk of bias, if there was insufficient information to assess whether the risk of bias of selective outcome reporting was present.

Incomplete outcome data (Attrition bias)

- Low risk of bias, if
  1. attrition rate was balanced between treatment arms and relatively low (below 20%), and
  2. reasons for discontinuation were described, and
  3. an intention-to-treat analysis was performed, and
  4. an appropriate method of imputation of missing outcome data was applied.
- High risk of bias, if
  1. withdrawal rates were unbalanced between treatment arms or more than 20%, or
2. reasons for drop-outs were not clearly described, or

3. an inappropriate analysis was performed (i.e. per protocol analysis), or

4. an inappropriate imputation method (i.e. last observation carried forward method) was used to handle missing data.

• Unclear risk of bias, if it is not clear whether there were any drop-outs, or reasons for these withdrawals are not clear, or no method of imputation of missing data is mentioned.

Pharmaceutical industry funding (Sponsor bias)²

• Low risk of bias, if the trial was not funded by a drug manufacturer.

• High risk of bias, if the trial was funded by a drug manufacturer.

• Unclear risk of bias, if the source of funding was unclear.

Author-industry financial ties and/or employment (Other bias)²

• Low risk of bias, if any authors did not disclose financial ties and/or employment by the pharmaceutical industry.

• High risk of bias, if any authors disclose financial ties and/or employment by the pharmaceutical industry.

• Unclear risk of bias, if author-industry financial ties or affiliation were not reported.

Reference

trials. BMJ. 2011;343:d5928.

**Item S3  Statistical method**


1. **Bayesian approach and Credible intervals (CrI)**

The Bayesian approach utilizes both sample data and prior knowledge in estimating validity and weights each in proportion to its information value. The sample information is combined with the prior distribution to produce a posterior distribution, the mean of which is then taken as the estimate of the parameter of interest, in this case, test validity. Confidence intervals—called credible intervals by Bayesians—can be placed around this mean\(^1\).

*Confidence intervals (CI)* usually is used in conventional non-Bayesian statistical analysis to indicate the precision of an estimate (for example, estimate of effect size). *Credible intervals (CrI)* in Bayesian statistics could be considered as analogous to confidence interval (CI) in non-Bayesian (or frequentist) statistical analysis, reflecting the precision of an estimate. A 95% credible interval can be interpreted as the following: there is 95% probability that the true treatment effect lies in a 95% credible interval.\(^2,3\)

2. **Model interpretation**

Defining \(r_{ik}\) as the number of events (occurrence of CI-AKI), out of the total number of patients in each arm, \(n_{ik}\), for arm \(k\) of trial \(i\), we assume that the data generation process follows a Binomial likelihood i.e.

\[
r_{ik} \sim \text{Binomial}(p_{ik}, n_{ik})
\]

where \(p_{ik}\) represents the probability of an event in arm \(k\) of trial \(i\) (\(i=1,2…139; k=1,2,3,4\)). \(p_{ik}\) can only take values between 0 and 1. We model the probabilities of
events $p_{ik}$ on the logit scale as

$$ \text{logit}(p_{ik}) = \mu_i + \delta_{i,jk} I_{k \neq 1} \tag{1} $$

where

$$ I_{(u)} = 1 \text{ if } u \text{ is true} $$

$$ I_{(u)} = 0 \text{ otherwise} $$

In this setup, $\mu_i$ are trial-specific baselines, representing the log-odds of the outcome in the ‘control’ treatment, $\delta_{i,jk}$ are the trial-specific log-odds ratios of events on the treatment group $k$ compared to $j$.

**Parameterization of the model:**

The probabilities of event in the arms of a study $p_{ik}$ can be parameterized in terms of the log-odds ratios (OR). The underlying trial-specific effect are defined as $\theta_{i,jk}$; the log(OR) of treatment $k$ relative to $j$ in study $i$.

**Random effects model:**

For a random effects model the trial-specific log-odds ratios come from a common distribution:

$$ \delta_{i,jk} \sim N (d_{jk}, \sigma^2) $$

where $d_{jk}$ is the multiple-treatments meta-analysis estimate of the relative effect of treatment $j$ relative to $k$ and $\sigma$ is the heterogeneity standard deviation assumed common across comparisons.

**Fixed effect model:**

For a fixed effect model we replace equation (1) with

$$ \text{logit}(p_{ik}) = \mu_i + d_{ik} I_{k \neq 1} $$
which is equivalent to setting the between-trial heterogeneity $\sigma^2$ to zero thus assuming homogeneity of the underlying true treatment effects.

**Consistency model:**

Assuming consistency, the means of the random effects distribution are related. Selecting $T-1$ basic parameters $\mu_{Ak}$, all means are related via $\mu_{jk} = \mu_{Ak} - \mu_{Aj}$.

**Inconsistency model:**

In a random effects inconsistency model, no association between the $\mu_{Ak}$s are assumed, so the model is a series of independent comparison-specific meta-analyses which however share the same heterogeneity parameter $\sigma^2$.

In a fixed effects inconsistency model no shared variance parameter needs to be considered. The inconsistency model is then equivalent to performing completely separate pairwise meta-analysis of the data.

**Meta-regression and subgroup model:**

The model specification considered is to assume that all treatment by covariate interactions (for all treatments vs the common control comparator) are identical; that is, the same regression coefficient ($\beta$) is assumed regardless of treatment (excluding control) implying the same covariate effect for each treatment relative to control. A prior distribution is given for the common regression coefficient.

$$
\delta_{ijk} \sim \begin{cases} 
\text{Normal}(d_{Ak} + \beta X_j, \sigma^2) & \text{if } b = A \\
\text{Normal}(d_{bk}, \sigma^2) & \text{if } b \neq A 
\end{cases}
$$
\[ r_{jk} \sim \text{Binomial}(p_{jk}, n_{jk}) \text{ for trial } j, \text{ treatment } k \]

\[
\logit(p_{jk}) = \begin{cases} 
\mu_{jb} & \text{if } k = b \\
\mu_{jb} + \delta_{jk} & \text{if } k \text{ alphabetically after } b 
\end{cases}
\]

\(\mu_{jb}\) is the log odds of an event in trial \(j\) on ‘baseline’ treatment \(b\), \(\delta_{jk}\) is the trial-specific log odds ratio of treatment \(k\) relative to treatment \(b\) in trial \(j\). The pooled log odds ratios, \(d_{bk}\), are identified by expressing them in terms of the reference treatment \(A\), \(d_{ak} - d_{ab}\), where \(d_{aa}\) is set equal to zero. The between-study variance \(\sigma^2\) is assumed constant for all treatment comparisons. \(^4\)

**SUCRA**

The treatments can be ranked according to their effectiveness. The order of treatment in every MCMC circle is calculated as

\[
\text{order}_k = \sum_{j=1}^{nt} I(d_j \leq d_k)
\]

where \(I(d_j \leq d_k) = 1\) if \(d_j \leq d_k\) and 0 otherwise. The probability of treatment \(k\) to be at the \(j\) order is estimated from the quantity \(\text{effectiveness}_{k,j}\) and the cumulative probabilities by \(\text{cum.effectiveness}_{k,j}\). Then the surface under the cumulative ranking curve (SUCRA) for the treatment is

\[
\text{SUCRA}_k = \frac{\sum_{j=1}^{nt-1} \text{cum.efficiency}_{k,j}}{nt - 1}
\]

3. **Model fit**

We checked whether a model’s fit is satisfactory using the deviance information criterion (DIC). DIC is the sum of \(Dbar\) (the posterior mean residual deviance) and the leverage, \(Pd\) (also termed the effective number of parameters). The model fits the data
adequately when $Dbar$ is approximative with the number of data points. $Pd$ provides a measure of model complexity. Then the DIC means a measure of model fit that penalizes model complexity – lower values of the DIC suggest a more parsimonious model.

In order to assess whether the model provided adequate fit, we calculated DICs of four models, including random consistency, random inconsistency, fixed consistency, fixed inconsistency model within a Bayesian framework using the WinBUGS and R software.

4. Assessment of inconsistency

A “direct” estimate of the C vs. B effect, $\hat{d}_{BC}^{dir}$, is to be compared to an “indirect” estimate, $\hat{d}_{BC}^{ind}$, formed from the AB and AC direct evidence

$$\hat{d}_{BC}^{ind} = \hat{d}_{AB}^{dir} - \hat{d}_{AC}^{dir}$$

$$Var(\hat{d}_{BC}) = Var(\hat{d}_{AB}^{dir}) + Var(\hat{d}_{AC}^{dir})$$

We assume that the direct estimates can either be estimates from individual trials. An estimate of the inconsistency, $\omega$, can be formed by simply subtracting the direct and indirect estimates:

$$\hat{\omega}_{BC} = \hat{d}_{BC}^{dir} - \hat{d}_{BC}^{ind}$$

$$Var(\hat{\omega}_{BC}) = Var(\hat{d}_{BC}^{dir}) + Var(\hat{d}_{BC}^{ind}) = Var(\hat{d}_{BC}^{dir}) + Var(\hat{d}_{BC}^{dir}) + Var(\hat{d}_{BC}^{dir})$$

An approximate test of the null hypothesis that there is no inconsistency can be obtained by referring $Z_{BC} = \frac{\hat{\omega}_{BC}}{\sqrt{Var(\hat{\omega}_{BC})}}$ to the standard normal distribution. the method can only be applied to 3 independent sources of data. Obviously, the method can only be applied to 3 independent sources of data. This idea can be extended to all loops formed in the
network and plot the ω together with its 95% confidence interval. In the presence of consistency within a loop all intervals should be compatible with zero.

Another way to infer about consistency in the network as a whole is to compare the DICs between the consistency and inconsistency model. If the DIC assuming inconsistency is lower than the DIC assuming consistency by three or more units, then the assumption of consistency is likely to be violated.

Reference:


